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REVIEW

Gout – management of a chronic disease: a systematic review

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Abstract

Objectives: Gout is the most common inflammatory arthritis of the 21 century, but is still frequently misdiagnosed. This review aims to provide guidance for gout management in clinical practice, which includes the diagnosis, treatment of acute episodes, but also long-term therapy to reduce serum urate, as well as lifestyle changes and prevention of recurrent episodes.

Design: Systematic review without meta-analysis.

Methods: We have systematically searched Google Scholar, PubMed, and all relevant worldwide guidelines to identify and select clinical guidelines for gout. We have included eligible gout articles according to predefined inclusion and exclusion criteria after selecting titles, abstracts and full texts. The characteristics of the recommendations reported in the guidelines included were extracted and analyzed.

Results: We selected 27 eligible papers and tried to facilitate the identification of recommendations for the treatment of gout in the acute phase, but also in the chronic phase. The recommendations were detailed and explained during this extensive review. Conclusions: Despite the availability of effective serum urate reduction therapies, overall gout management is poor. Achieving therapeutic goals is often low both at the initiation of therapy and in long-term treatment. Optimal strategies for managing gout are necessary in both acute and chronic gout flames in patients who are prone to the development of this pathology.

Keywords: gout, arthritis, hyperuricemia

Introduction

Also known as the disease of the kings, gout represents one of the oldest joint disease and the best-known inflammatory arthritis with a high prevalence worldwide (4% of adults) [**1,2**]. It was described for the first time in 2640 B.C. and it remained the most haunting human arthritis [**1**]. In 2006, the diagnosis for gout was defined by the first EULAR recommendations [**2**].

The prevalence of gout has recently increased in all developed countries due to lifestyle and comorbidities. This pathology is more common in men, especially with aging (over 40 years) [**3,4**]. Women are protected

during premenopause due to the uricosuric effect of estrogen, progesterone and decreased insulin resistance [**3,4**].

Our team's researchers also searched Google scholar and PubMed publications on gout and "hyperuricemia" as keywords and selected a number of 120 publications by title and abstract (**Fig. 1**). Two researchers (PVF, SLD) independently filtered the titles and abstracts of the initially identified literature, then selected the fully eligible text articles (n=47) (**Fig. 1**). Disagreements were resolved by face-to-face discussions in consultation with a third researcher (CSP). Our team discussed and planned the data extraction by conducting a preliminary identification study, the structure and content of the recommendations, the motivation and explanation of the recommendations and other information in the included guidelines (27 papers) (**Fig. 1**).

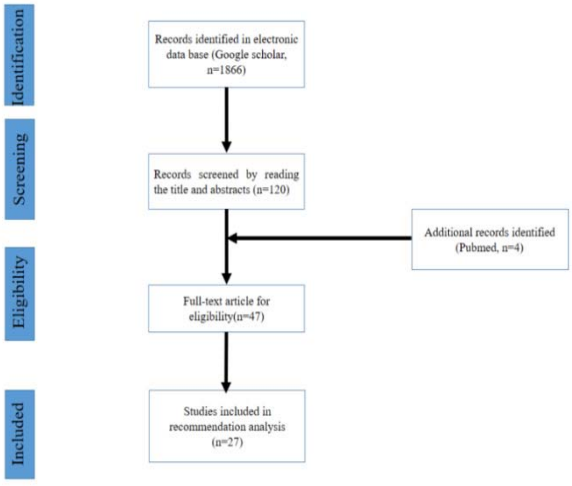

Fig. 1 Flow diagram of the search and selection of eligible papers

Gout is caused by the chronic elevation of serum uric acid and deposition of monosodium urate crystals in tissues and synovial fluid [**1,2**]. Clinical manifestations of gout result from the deposition of monosodium urate crystals producing recurrent cellulitis and acute bursitis, chronic arthritis, tophi, as well as urolithiasis and chronic kidney disease [**5**].

The deposition of urate crystals generates a complex immune cascade producing the release of several cytokines, as well as the recruitment of neutrophils causing inflammation and severe pain [**6,7**]. Tophi represent subcutaneous nodules composed of monosodium urate crystals in a matrix of lipids, proteins and mucopolysaccharides [**7**]. The affected joints are the first metatarsophageal joint, midtarsal joints, wrists, ankles, knees, fingers and elbows [**7**].

Clinical manifestations supporting a clinical diagnosis of gout are the frequent involvement of the first metatarsophageal joint with rapid onset of pain, severe edema and erythema, previous episodes of acute arthritis, associated cardiovascular disease, hyperuricemia and male gender [**2**]. It is important to know that the presence of hyperuricemia alone does not establish the diagnosis of gout, but we must look for associated comorbidities and risk factors like cardiovascular disease [**2**].

Risk factors such as age, male gender, menopausal status in women, high blood pressure, impaired renal function, and comorbidities that include metabolic syndrome are all associated with lower uric acid excretion [**5**]. Also, chronic antihypertensive treatment that includes diuretic, low-dose aspirin, cyclosporine, alcohol consumption, and lead exposure are associated with decreased uric acid excretion [**5**].

Lifestyle can represent a risk factor for gout, but also for other chronic diseases with public health importance. The consumption of alcohol drinks (particularly beer), beverages sweetened with high-fructose and fruit juice and also corn syrup, some seafood (e.g. shellfish, some large saltwater fish) and meat (especially red meat, wild game, and organ meat) represent an increased risk for developing gout [**7**]. Studies show that foods rich in purine, such as oatmeal, nuts, legumes, mushrooms and asparagus, do not increase the risk, and dairy products provide easy protection against gout [**8**]. Also, genetic mutations, such as some defects in the renal

urate transport system, can more frequently cause uric acid underexcretion and less often overproduction, leading to gout [**7**].

Clinical presentations

The diagnosis of gout is usually clinically established on the basis of the rapid development of single-jointed arthritis, characterized by red, tender, warm and swollen joints and with clinical resolution within a week, that usually involves the first metatarsophalangeal joint (more than 75% of gout arthritis), also known as podagral (podagra) [**7,9**]. Flares of gout could be precipitated by dehydration, injury, infection, initiation of ULT, excess of alcohol or purine intake [**3**]. Chronic gout is often polyarticular and characterized by underlying pain between attacks and accumulations of uric acid, known as tophi [**9**].

For the diagnosis of gout, the most often used criteria in Europe are those developed by the European League Against Rheumatism that were updated in 2018 (**Table 1**) [**2**]. Microscopic examination of joint fluid is less commonly used and reveals monosodium urate crystals in shape, preferably intracellular, with bright, negative birefringence, on light compensated polarized light microscopy [**7**]. Radiographic changes are not common in the initial forms of the disease, they take several years to develop and are necessary to establish a positive diagnosis in the later stages of gout [**3**].

*Table 1. EULAR Update - Eight recommendations for the diagnosis of gout [**2**]*

	EULAR RECOMMENDATIONS	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
1.	It is recommended to look for crystals in synovial fluid or aspirated from tophi in each person suspected of gout, because highlighting the MSU crystals establishes the definitive diagnosis of gout.	**2b**	**B**
2.	Gout should be considered in any adult with arthritis. If synovial fluid analysis is not possible, the clinical diagnosis is supported by the following suggestive (but not specific) features: involvement of a single leg joint (especially the first metatarsophalangeal joint) or ankle joint; rapid onset of severe pain and edema (< 24 hours); erythema; similar previous episodes of acute arthritis; masculine gender, hyperuricemia and associated cardiovascular disease.	**2b**	**B**
3.	Hyperuricemia alone does not diagnose gout.	**2a**	**B**
4.	A strong recommendation is to aspirate and examine synovial fluid of all the patients with undiagnosed inflammatory arthritis.	**3**	**C**
5.	When the clinical diagnosis is uncertain and it is not possible to identify uric acid crystals, imaging is necessary to look for the deposition of crystals, but also to make a differential diagnosis.	**1b**	**A**
6.	Simple radiographs are needed to look for imaging evidence of crystal deposition, but with limited value for the diagnosis of acute gout. Joint ultrasound may be more useful in diagnosing patients with acute or chronic gout, tophi that are not evident on clinical examination or the presence of a double contour of the cartilage surface (ultrasound pathognomonic sign of urate deposits in the joints).	**1b**	**A**

7.	Patients who are diagnosed with gout should be evaluated for risk factors such as hyperuricemia, especially overweight/ obese, medication (including diuretics, cyclosporine, low-dose aspirin, tacrolimus), chronic kidney disease; diet rich in meat and shellfish, excessive alcohol consumption (especially beer and spirits).	**1a**	**A**
8.	Patients with gout should be evaluated systematically for the presence of comorbidities such as obesity, hypertension, dyslipidemia, diabetes, ischemic heart disease, heart failure and kidney failure.	**1a**	**A**

EULAR = European League Against Rheumatism; MSU = monosodium urate

X-rays may show:

o Swelling of the soft tissues during acute or tophaceous gout;

o Preservation of joint space until late illness;

o Absence of bone proliferation;

o Increased density/ calcification of soft tissues in tophaceous gout – eccentric;

o Cortical erosions - intra-articular, well defined, marginal, distant from the articular line, with sclerotic and overhanging edges.

Imaging examination by ultrasonography, computed tomography or magnetic resonance imaging is not usually required for diagnosis [**7**]. Ultrasound characteristics of gout include the double mark of the cartilaginous contour (urate crystals are deposited at the level of the surface of the hyaline articular cartilage), hyper-echoic aggregates, intra-articular and intra-bursal tophi [**3**].

Gouty arthritis, but also tophi cause chronic disabilities, low productivity, increased use of health care resources and affect the quality of life of patients [**5**]. Therefore, gout represents a major public health problem [**10**]. It is not yet clear whether the impact of gout on the patient's life is correlated with the disease itself or the associated risk factors or medical conditions [**10**]. Recurrent flares of gout arthritis are associated with chronic arthritis and tophi, recent use of diuretic drugs and alcohol consumption [**5**].

The differential diagnosis

Pseudogout, trauma and infections are included in the differential diagnosis of monoarticular arthritis [**7**]. Pseudogout (or "false gout") is a form of arthritis that results from deposits of calcium pyrophosphate crystals, and commonly affects the knees and wrists [**7**]. Swelling of the joint associated with trauma is usually identified from the history; however, trauma can lead to the onset of acute gout caused by increased concentrations of urate at the synovial level [**7,9**]. It is necessary to exclude a fracture in a patient with gout-like symptoms by imaging examination especially if he has a traumatic joint injury associated [**7,9**].

Septic arthritis can occur without fever or leukocytosis, so it is necessary to perform arthrocentesis to differentiate this condition from an acute outbreak of gout [**7,9**]. In exceptional cases, septic arthritis and gout may begin at the same time [**3,7,11**]. Another inflammatory arthritis that mimics the clinical presentation of gout could be psoriatic arthritis, reactive arthritis, rheumatoid arthritis or osteoarthritis [**3**].

Management of gout

Recommendations for the management of acute attacks

To understand the importance of treating acute episodes of gout, patients must be educated [**5**]. Rapid and complete remission of symptoms requires that the treatment of the gout episode begins no later than 24 hours after the onset of symptoms. Acute flares of gout can be treated with NSAIDs, colchicine and oral or intravenous corticosteroids [**5**]. The

first-line treatment of the acute episode should take into account the patient's choice, renal function and associated comorbidities [**5**].

In addition, the affected joint requires the drug treatment and a cold environment (application of ice packs) [**5**]. Also, the recommendation of rest of the affected joints is based on the vast experience of the patients and on the opinion of the experts [**5**]. Ice packs can be used as the sole treatment for acute gout or when medicines are contraindicated due to multiple comorbidities [**5**].

The recommendation of using topical ice in combination with prednisolone and colchicine is supported by a Cochrane systematic review of a single small RCT (n = 19) [**12**]. This study showed that the use of ice packs produces a significant reduction in pain without associating additional adverse events (3.3 cm, 95% CI: 5.84 to 0.82 on 10 visual analogue scale) [**5**].

Patients with an acute gout attack should receive high-dose NSAIDs due to the severity of pain and inflammation and continued treatment for up to one to two days after the symptoms have improved [**7,13-15**]. However, NSAIDs should be used with caution and are contraindicated in patients with peptic ulcer, history of gastrointestinal bleeding or perforation or renal failure [**5**]. COX-2 inhibitors show equal efficacy and superior gastrointestinal tolerability to non-selective NSAIDs, with the statement that there are uncertainties in the chronic administration of their cardiovascular and renal toxicity [**5,16,17**]. It is recommended that patients receiving anti-inflammatory treatment (NSAIDs or cyclooxygenase-2 inhibitors, corticosteroids) should also receive a gastro-protective agent [**5**].

Prevention of recurrent acute episodes of gout does not include a long-term treatment with NSAIDs and corticosteroids without combining a medication to reduce uric acid, because the absence of clinical signs of inflammation does not imply the absence of continuous deposition of acid crystals and also joint accumulation and damage [**18**]. If a patient has an acute episode of gout, chronic uric acid reduction medication will not be discontinued, being continuously administered [**19**].

Allopurinol (medicine used to reduce urate) in combination with an NSAID and colchicine can also be administered in the acute outbreak, even if it was previously thought that this drug aggravates the flare [**7,20**]. Once the uric acid level is below the target values, treatment should continue for at least 3 months in patients without tophi and for at least 6 months in those with tophi [**19**].

Corticosteroids are the alternative medication for those patients with low tolerability to NSAIDs or colchicine [**5**]. Short-term corticosteroids can be administered to diabetic patients with adequate monitoring of hyperglycaemia [**5,7,9**]. For patients with acute monoarticular disease and associated comorbidities, joint aspiration and injection of a corticosteroid are preferred, which are extremely effective and are the first-line option [**5,7,9**].

Particular attention should be given to discontinuation of corticosteroid therapy for acute episodes of gout due to the frequent rebound effects [**7**]. To reduce the risk of a flare-up, preventive treatment and a gradual reduction of the dose of corticosteroids until 10 to 14 days after the onset of symptoms is recommended [**7**].

Option treatment for acute flare gout is colchicine, but without analgesic properties and with increased efficacy if is administered within the first 72 hours from onset [**7**]. Terkeltaub's study showed that low doses of colchicine (1.2 mg initially and 600 mg per hour) are just as effective and have fewer side effects (nausea, vomiting, diarrhea), as a dose of more than 4,8 mg at over 6 hours [**5**]. Colchicine doses should be reduced in elderly patients and those with an estimated

glomerular filtration rate (eGFR) of < 10 ml/ min/ 1.73 m² and contraindicated in those with eGFR of 10-50 ml/ min/ 1.73 m² [**5**].

Patients with treatment standard failure of acute gout can receive IL-1 inhibitors (anakinra, canakinumab and rilonacept) [**5**]. IL-1 inhibitor treatment has been approved by the European Medicines Agency (EMA), but has not been approved in the United States (Food and Drug Administration - FDA) and the United Kingdom (National Institute for Excellence in Health and Care – NICE) [**5**].

Dietary modifications

Overweight patients should have a gradual weight loss (approximately 10% of weight in a year) followed by weight maintenance. Patients with gout should be encouraged to have a well-balanced diet, rich in vegetables and fiber, low in fat and sugar and also to exercise.

The major risk factor for gout in men is weight gain so that weight loss is necessary, the same as stopping the use of high-fructose corn syrup, rich purine animal protein (organ meats, lamb, pork, beef, shellfish) and alcohol [**7**]. The diet is based on skim milk and/ or low-fat yogurt, vegetable sources of protein, including beans and soy, but also cherries [**5**]. In a study of 633 subjects with gout, it was observed that patients who consumed cherries and cherry extract had a significantly lower risk of gout attacks (35%) compared to no intake [**5,21**]. The combination of cherries and allopurinol reduces the risk of acute gout outbreaks by 75% (odds ratio (OR) = 0.25, 95% CI: 0.15, 0.42) [**5**].

Patients are encouraged to avoid dehydration and to drink more than 2 l of water per day, especially those with gout and a history of urolithiasis [**5**]. Patients with recurrent urolithiasis are recommended to alkalize their urine with potassium citrate (60 mEq per day) [**5**]. All the patients with gout must be screened for cigarette smoking and comorbidities conditions such as hypertension, dyslipidemia, diabetes mellitus and renal disease [**5**]. These patients should be reviewed and managed accordingly [**5**].

Prevention for chronic and recurrent gout attacks

Serum urate reduction therapy is recommended in patients who have any of the following: at least two acute episodes per year (one per year in people with chronic kidney disease in stage 2 or older), tophi or a history of nephrolithiasis and for the prevention of recurrent gout attacks [**7**]. Level of serum urate must be lower than 5 to 6 mg per dL (297 to 357 µmol per L) [**3,7,9,22**]. Uric acid reduction therapy should be continued for up to 3-6 months after the onset of symptoms and, if signs or symptoms are present, therapy should be continued for an indefinite period [**7,22**].

The first therapeutic line to prevent recurrent gout is a xanthine oxidase inhibitor, allopurinol [**14**]. Prevention of chronic disease progression in patients with gout and associated comorbidities, such as chronic kidney disease or congestive heart failure, is achieved with the help of allopurinol [**23,24**]. It is recommended that the initiation dose is 100 mg daily and that the dose is gradually increased to 300 mg daily so that the serum uric acid level is below the reference value [**7**]. Some patients may receive doses higher than 300 mg a day, even if they are associated with kidney damage, but who require close monitoring for adverse effects [**14**].

To prevent recurrent gout, the first line of treatment is Febuxostat, another xanthine oxidase inhibitor approved by the FDA in 2009 [**14**]. A dose higher than 300 mg of allopurinol is needed to reduce serum uric acid, but it is not more effective in reducing the frequency of acute episodes [**25,26**]. The optimal dose of febuxostat is 40 mg per day, and for patients with a serum uric acid level > 6 mg/ dL, the dose could be increased to 80 mg per day [**25,26**]. It is not recommended for use in

patients receiving immunosuppressive therapy (mercaptopurine and azathioprine) [**25,26**].

Probenecid is the second line of treatment due to the numerous drug interactions and its effect is to increase the urinary excretion of uric acid [**7**]. When a drug does not independently lower serum uric acid to target levels, probenecid can be used in combination with allopurinol or febuxostat [**7**]. The most common side effect that can be prevented by increasing oral hydration and alkalization of urine with potassium citrate is urinary stones [**14**]. Special care should be taken in patients taking methotrexate and ketorolac, as probenecid increases their serum levels, leading to toxicity [**7**].

Pegloticase is a third-line uricase and can be used in refractory cases [**27**]. It metabolizes uric acid into allantoin and is administered intravenously [**27**]. Treatment is prescribed only by a rheumatologist and is administered every two weeks, which involves high costs (> $ 5,000 per dose) [**7**].

Conclusion

Despite the major advances made by the medical world in understanding pathogenesis and therapeutic advances, the prevalence of gout is increasing. Although the long-term strategy of decreasing serum urate concentrations is extremely effective in removing uric acid crystals, this pathology still remains poorly controlled. Every patient must benefit from a treatment strategy to prevent the serious consequences of this disease on short and long term.

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Conflict of interest
The authors declare no conflict of interest.

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